Advanced Drug Delivery Reviews 128 (2018) 132–147

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

MEMS devices for drug delivery☆

Hyunjoo J. Lee [a], Nakwon Choi [b,c], Eui-Sung Yoon [b], Il-Joo Cho [b,c,*]

[a] School of Electrical Engineering, Korea Advanced Institute of Science and Technology, Daejeon 34141, Republic of Korea
[b] Center for BioMicrosystems, Brain Science Institute, Korea Institute of Science and Technology (KIST), Seoul 02792, Republic of Korea
[c] Division of Bio-Medical Science & Technology (Biomedical Engineering), KIST School, Korea University of Science and Technology (UST), Daejeon 34113, Republic of Korea

ARTICLE INFO

Article history:
Received 20 May 2017
Received in revised form 6 September 2017
Accepted 2 November 2017
Available online 5 November 2017

Keywords:
Brain infusion
Blood-brain barrier (BBB) disruption
Capsule endoscope
Implantable drug delivery
Microneedles
Transdermal drug delivery

ABSTRACT

Novel drug delivery systems based on microtechnology have advanced tremendously, but yet face some technological and societal hurdles to fully achieve their potential. The novel drug delivery systems aim to deliver drugs in a spatiotemporal- and dosage-controlled manner with a goal to address the unmet medical needs from oral delivery and hypodermic injection. The unmet needs include effective delivery of new types of drug candidates that are otherwise insoluble and unstable, targeted delivery to areas protected by barriers (*e.g.* brain and posterior eye segment), localized delivery of potent drugs, and improved patient compliance. After scrutinizing the design considerations and challenges associated with delivery to areas that cannot be efficiently targeted through standard drug delivery (*e.g.* brain, posterior eye segment, and gastrointestinal tract), this review provides a summary of recent advances that addressed these challenges and summarizes yet unresolved problems in each target area. The opportunities for innovation in devising the novel drug delivery systems are still high; with integration of advanced microtechnology, advanced fabrication of biomaterials, and biotechnology, the novel drug delivery is poised to be a promising alternative to the oral administration and hypodermic injection for a large spectrum of drug candidates.

Contents

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Microfluidic Devices for Drug Delivery Systems".

* Corresponding author.
E-mail address: ijcho@kist.re.kr (I.-J. Cho).

https://doi.org/10.1016/j.addr.2017.11.003
0169-409X/

1. Introduction

With the rapid development in novel pharmaceutical compounds and intervention, there is an increasing need for novel drug delivery systems that can address challenges associated with conventional drug delivery systems. For example, modern drug candidates include a wide spectrum of molecules including large biomolecules (*e.g.* peptides and proteins) with low bioavailability, small molecules with poor water solubility, and potent drugs with narrow therapeutic windows. Due to this wide range of physiochemical and pharmacokinetic properties of the modern drug candidates, conventional oral or intravenous administration might not be the most suitable route of administration. Evaluation of drug candidates and optimization of drug developments are thus limited by a lack of adequate delivery systems. In addition, with advances in diagnostic techniques, drug delivery is not limited only to wound healing and immunology but is applicable to cancer treatment, gene delivery, and insulin delivery [1], which requires targeted drug delivery with controlled release. There are also areas in our body such as the brain and the posterior eye segment that are significantly challenging sites to target through conventional intravenous administration due to the physical barriers (*i.e.* BBB and blood-retinal barrier) that separate the organs from blood circulation. One method to overcome these difficulties is to formulate nanoscale delivery vehicles to enable site-specific targeted drug delivery with a goal for oral delivery of proteins, peptides, and even imaging nanoprobes [2–4]. Nanoparticle-based drug delivery enables targeted drug delivery to the desired regions but reliable encapsulation of drugs in the nanoparticle with desired release characteristics are challenging to achieve [5].

Microtechnology or Microelectromechanical Systems (MEMS) is another promising technology for developments of the novel drug delivery systems that overcome the current challenges and accommodate a vast variety of drug delivery applications. By offering miniaturization [4–7], integrations of multiple functions [8,9], and electromechanical control [10–12], microtechnology allows delivery of a wide range of drugs with high therapeutic efficacy. Also, microtechnology enables localized drug delivery to challenging areas in our body by means of alternative routes of administration. For instance, microneedle technology for transdermal drug delivery is one of the successful applications of microtechnology. Microneedle technology now in the third generation of development accommodates delivery of RNA and vaccine [13,14] and strives to achieve active control of drug release through smart triggering systems [8]. Using MEMS technology, hundreds of thin microneedles can be precisely manufactured in a single array to deliver drugs without incurring damage and pain. In addition, while the conventional drug delivery relies mostly on diffusion, MEMS micropump technology allows active control over drug release such as release rates and infusion volumes and provides means to continuously supply drugs through a reservoir [15]. Furthermore, the agile interface between a microtechnology component to electronic components greatly expands the efficiency and functionality of the novel drug delivery systems.

Table 1
Summary of MEMS devices utilized in novel drug delivery systems and the associated remaining challenges for systems targeting different body areas.

Target area	MEMS devices		Remaining challenges
Brain	Implantable	Neural probes/microneedles [9,26,27,30–33,36–38]	• Biocompatibility • Systematic errors (leakage, clogging, biofouling)
	Noninvasive	Ultrasound transducers [57–59,63,64]	• Multi-functionalities • Miniaturization • Higher control over ultrasound parameters
Eye	Implantable	MEMS pumps, reservoir, polymeric inserts [76–83,85–90]	• Choric robustness • Drug volume • Removal • On-demand activation
	Noninvasive	Therapeutic contact lens [73]	• Interaction between drugs and contact lens materials • Preserving transparency
GI	Oral	Capsule endoscope [100–114]	• Reliable anchoring and actuation mechanism • Batteryless activation
Skin	Implantable	Subcutaneous MEMS pumps, reservoir, polymeric inserts [137–144]	• Biocompatibility • Drug volume • Removal • Self-administrated release
	Minimally invasive	Transdermal microneedles [8,14,125–127,129]	• Closed-loop release • On-demand release • Multi-functionalities • Chronic uses (clogging, biofouling)